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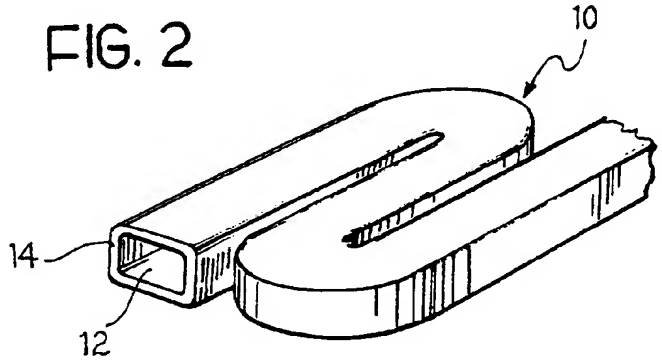
(54) A stent for angioplasty and a production process therefor

(57) The stent for angioplasty has a body (10) in the form of a generally tubular casing capable of being dilated in use from a radially-contracted position to a radially-expanded position. The body (10) includes a support structure (12) made from a first material capable of withstanding this dilation without losing its structural integrity. A structure (14) made from a second material which has been rendered radioactive following the exposure of the stent itself to a neutron flux is associated with at least a portion of the carrying structure (12).

FIG. 2



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Description

The present invention generally concerns so-called stents for angioplasty.

This term is intended generally to indicate devices intended for endoluminal application (for example, within a blood vessel) usually effected by catheterisation, with the subsequent expansion in place for the local support of the lumen. The principal aim of this is to avoid the reestablishment of a stenotic sits at the treated site. It should be noted that the use of substantially similar structures to effect the expansion and anchorage in place of vascular grafts has already been proposed in the art: naturally, this possible extension of the field of application should also be seen as being included within the ambit of the invention.

For a general review of vascular stents, reference may usefully be made to the work "Textbook of Interventional Cardiology" edited by Eric J. Topol, W. B. Saunders Company, 1994 and, in particular, to section IV of volume II, entitled "Coronary stenting".

Many patent documents have addressed this problem, such as, for example, US-A-4 776 337, US-A-4 800 882, US-A-4 907 336, US-A-4 886 062, US-A-4 830 003, US-A-4 856 516, US-A-4 768 507, and US-A-4 503 569.

One problem that is not yet completely resolved in connection with the implantation of a stent is in relation to restenosis which, depending on the type of lumen in question, may be more or less likely to occur. Several studies have shown that the principal mechanism causing restenosis after the stent-implantation operation is a hyperplasia of the neointima mediated by the cells of the smooth muscle.

It has, however, been noted that nuclear radiation, in particular β-radiation, inhibits the formation of the neointima. The manufacture of a stent capable of emitting nuclear radiation has therefore already been proposed: in this way, after implantation, the surrounding tissues become irradiated, which inhibits the above-mentioned hyperplasia.

To this end, atoms of the P^{32} radionuclide are injected, by means of a cyclotron, onto the surface of a stent made from conventional material, for example, stainless steel, before it is implanted (see "Radioactive Stents for the Prevention of Neointimal Hyperplasia" by Tim A. Fischell, from "Endoluminal Stenting" chapter 18, p. 134 (1996) edited by W. B. Saunders Company Ltd).

According to a similar technique (see "Technical and Engineering Aspects of Stents Which May Be Either Permanent or Removable" by R. Makkar et al., from "Endoluminal Stenting", chapter 32, p. 230, (1996) edited by W. B. Saunders Company Ltd), a titanium stent is bombarded with protons having an energy equal to 8 MeV, which provoke the reaction $Ti^{48}(p,n)V^{48}$, also leading in this case to the formation of a radioactive nuclide.

These methods require the use of very complicated equipment, such as a cyclotron, for accelerating the charged particles. In addition, since these particles are retained on the surface layer of the stent body, a sophisticated system must be provided for moving this latter in order to expose as much as possible of its surface to the particle beam.

Overall, therefore, these known techniques, although valid for research, are not suited to the mass production of radioactive stents.

The object of the present invention is that of overcoming the aforesaid disadvantages, and the invention has the characteristics referred to specifically in the following claims.

In the stent of the invention, the properties of the two different materials from which they are formed are exploited to best advantage: in particular, the first material gives the stent the desired mechanical properties and structural strength, while the second material enables the emission of nuclear radiation with the aforesaid advantages relating to the effect of inhibiting the formation of the neointima.

The materials conventionally used for stent production may be used as a first material, for example, stainless steel, while tantalum, iridium and mixtures thereof are preferred as the second material.

The choice of second material may be dictated by considerations of its compatibility with the first material, by the size of the desired activation section, and by the characteristics of the radionuclide which forms following exposure to the neutron flux.

The basic technique for the manufacture of this stent constitutes a factor which is in itself non-influential in the context of the invention, which is applicable irrespective of whether the stents are formed from a wire or a microtube.

Achieving the radioactivation of the second material by means of neutrons has significant operative advantages when compared with the known methods which require the use of charged particles.

In the first instance, the neutrons are generated in conventional fission reactors which are more widespread and easily understood than particle accelerators. These reactors also produce very high neutron fluxes (up to $10^{14}n/cm^2*s$), so that the radioactivation can be achieved in a very short time period.

Secondly, unlike charged particles, neutrons are not actually absorbed by the materials ordinarily used for the body of the stent. Therefore, the radioactivation treatment according to the invention can be effected without turning or otherwise moving the stent, but simply by exposing it to the neutron flux which is capable of activating even the portions of the second material not directly exposed to it after having passed through portions of the first material.

Further advantages and characteristics of the present invention will become clear from the following detailed description given by way of non-limitative

example and with reference to the accompanying drawings, in which:

Figure 1 is a general perspective view of a stent formed according to the invention;
Figure 2 is a view on an enlarged scale of a detail of Figure 1;
Figure 3 is a diagram on a logarithmic scale which shows the activity of several radionuclides as a function of the time elapsed since their activation;
Figure 4 is a view of a detail of a stent according to a different embodiment of the invention; and
Figure 5 is a view of a detail of a stent according to a further embodiment of the invention.

A stent (Figure 1) has a body 10 comprising a generally tubular casing with a wall having a looped or mesh-like apertured structure, an example of which can be seen on an enlarged scale in Figure 2. The body 10 is capable of being dilated in use from a radially-contracted position to a radially-expanded position. It includes (Figure 2) a support structure 12 made of a first material capable of withstanding this dilation without losing its structural integrity. The support structure 12, for example, made from AISI 316 L steel, is obtained from a microtube that is subsequently subjected to an operation for cutting the apertures, using known methods which form the subject of a fairly extensive body of literature and which do not therefore require detailed description in this context.

A layer 14 of Ta of a thickness equal to approximately 1/100 of the thickness of the body, which is usually between 0.07 and 0.1 mm, is deposited over the entire outer surface of the support structure 12. The layer 14 may, for example, be deposited using a PVD (Physical Vapour Deposition) process effected under vacuum with sputtering apparatus or using galvanic techniques.

Therefore, by exposing the coated stent to a neutron flux, for example, within a fission reactor, radioactive nuclides are generated, principally in relation to the tantalum nuclei according to the reaction $Ta^{181}(n,\gamma)Ta^{182}$.

Similar reactions also take place in relation to the Fe^{58} and Cr^{50} nuclei present in the steel of the support structure, leading to the formation of the radioactive nuclides Fe^{59} and Cr^{51}, although to a lesser extent than for tantalum.

The equation which expresses the variation over time of the activity of a given radio-isotope (expressed as the number of disintegrations per unit of time) is as follows:

$$A_i = \frac{m_i p_i}{M_i} N.\sigma_i \Phi (1-e^{-\lambda_i t_1}) e^{-\lambda_i t_2}$$

in which:

A_i = the activity (disintegrations/sec) of the radionuclide
p_i = isotopic percentage
m_i = mass of the element i(g)
M_i = atomic mass
N = Avogadro's number
σ_i = cross section (cm^2)
Φ = neutron flux ($n/cm^2 \cdot s$)
λ_i = decay constant = $0.693\ T_{1/2}$
t_1 = time of irradiation
t_2 = time since the end of the irradiation.

By utilising this equation, the graph shown in Figure 3 is obtained, which shows the variation in the activity (expressed in arbitrary units) of the main radionuclides (Fe^{59}, Cr^{51}, Ta^{182}) which form following the neutron irradiation of a stent of the type described above, as a function of the time elapsed since the irradiation.

It should be noted that, after several months, the only significant activity is that of the Ta^{182} which emits β radiation of maximum energy equal to 0.43 MeV and has a half life of 112 days. This medium-energy and low-duration radiation is particularly suitable for inhibiting restenosis.

From the knowledge of the patterns of decay of the type shown in Figure 3, and the optimal value for the medical applications of radioactive activity, it is therefore possible to determine the most favourable moment for the implantation of a stent that has been subjected to the radioactivation treatment described above.

When waiting for the appropriate moment, the stent can be subjected to other operations such as being coated with a highly biocompatible carbon film or, if not done previously, packaging and sterilisation.

By repeating the operations described above, but replacing the layer of tantalum with a 1 μm thick layer of iridium, a radioactive stent is obtained following the formation of the radionuclide Ir^{192}, whose variation in activity over time can be determined by considering the related line in Figure 3.

Ir^{192} also emits β radiation, although of much greater energy (0.68 MeV), and with a shorter half life (74.5 days) than the Ta^{182}. Utilising iridium enables a greater depth of penetration by the radiation over a shorter period of time to be achieved.

Figure 4 illustrates a wire utilisable with known techniques for the production of a stent having properties similar to that described above. In this case also, it has an internal support structure 12 made from AISI 316 L steel, which may be coated, for example, using sputtering or galvanic techniques, with a layer 14 of tantalum or iridium which is subsequently radioactivated by operations similar to those described above.

According to the invention, it is also possible to reverse the positions of the support structure and the radioactive structure in the wire, so that this latter is positioned on the inside. A wire of this type can, for example, be formed using coextrusion techniques of the

DFT (Drawn Fillet Tubing) type.

Figure 5 shows a further embodiment of the present invention. In this case, the structure 14 of the second radioactivatable material is made in the form of a plurality of inserts housed in respective recesses formed on the surface of the support structure 12. The inserts can be attached to the support structure using known techniques of welding, mounting, inclusion and the like.

Naturally, it is understood that while the principle of the invention remains the same, the details of manufacture and the embodiments may be widely varied with respect to those described above, without by this departing from the ambit of the present invention.

Claims

1. A stent for angioplasty having a body (10) in the form of a generally tubular casing capable of being dilated in use from a radially-contracted position to a radially-expanded position, the said body (10) including a support structure (12) of a first material capable of withstanding this dilation without losing its structural integrity, the said stent being characterised in that a structure (14) made from a second material which is made radioactive following the exposure of the stent itself to a neutron flux is associated with at least a part of the support structure (12).

2. A stent according to Claim 1, characterised in that the said structure (14) made from the second material constitutes a continuous layer coating at least a portion of the said support structure (12).

3. A stent according to Claim 2, characterised in that the said structure (14) made from the second material forms a continuous layer coating the entire support structure (12).

4. A stent according to Claim 2 or Claim 3, characterised in that the said coating layer is between 0.4 and 1 μm thick.

5. A stent according to Claim 1, characterised in that the said structure (14) made from the second material forms a core within the said support structure (12).

6. A stent according to Claim 5, characterised in that the said core has a diameter of between 10 and 100 μm.

7. A stent according to Claim 1, characterised in that the said structure (14) made from the second material is made in the form of a plurality of inserts housed in associated recesses formed on the surface of the support structure (12).

8. A stent according to any preceding claim, characterised in that the said second material is iridium, tantalum or mixtures thereof.

9. A method for the production of a stent having a body (10) in the form of a generally tubular casing capable of being dilated in use from a radially-contracted position to a radially-expanded position, the said method being characterised in that it provides for the association of at least a portion of the support structure (12) made from a first material and capable of withstanding this dilation without losing its structural integrity, with a structure (14) made from a second radioactivatable material, and of subsequently exposing the body (10) thus formed to a neutron flux so as to render the second material radioactive.

10. A method according to Claim 9, characterised in that the said association of the radioactivatable structure (14) with the support structure (12) is achieved by means of galvanic techniques or sputtering.

11. A method according to Claim 9, characterised in that the said association of the radioactivatable structure (14) with the support structure (12) is achieved by means of coextrusion.

12. A method according to Claim 9, characterised in that the said association of the radioactivatable structure (14) with the support structure (12) is achieved by means of welding, mounting or inclusion.

13. A method according to any of Claims 9 to 12, characterised in that the said body (10) is covered with a carbon film.

14. An intermediate product obtainable in the course of the method for the production of a stent according to any of Claims 9 to 13, having a body (10) in the form of a generally tubular casing capable of being dilated in use from a radially-contracted position to a radially-expanded position, the said body (10) including a support structure (12) made from a first material capable of withstanding this dilation without losing its structural integrity, and having associated with at least a portion thereof a structure (14) made from a second material which is capable of being rendered radioactive following its exposure to a neutron flux.

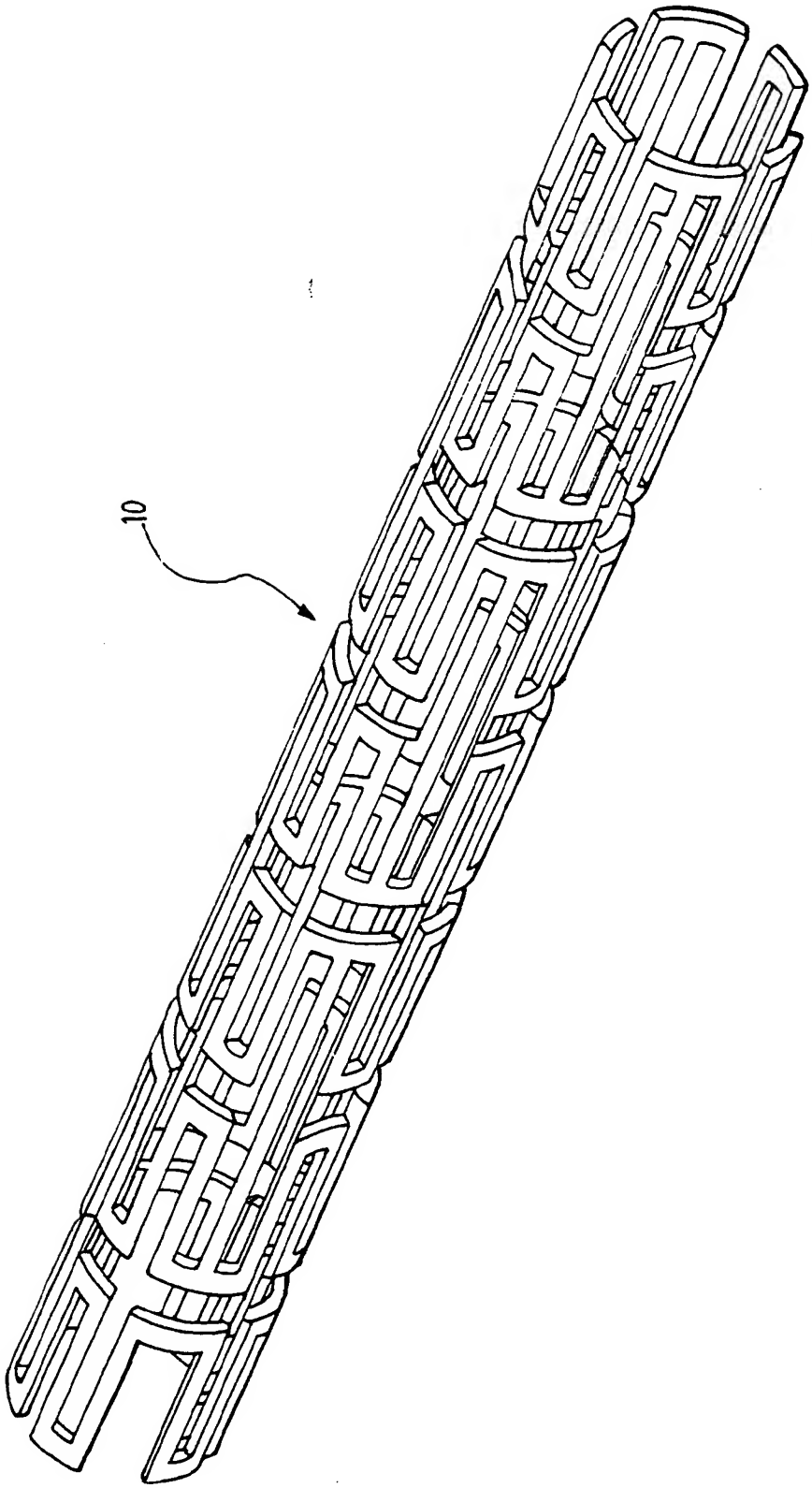


FIG. 1

FIG. 2

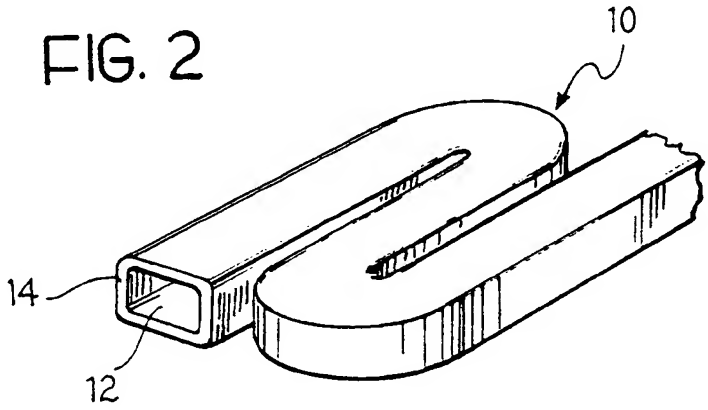

10
14
12

FIG. 3

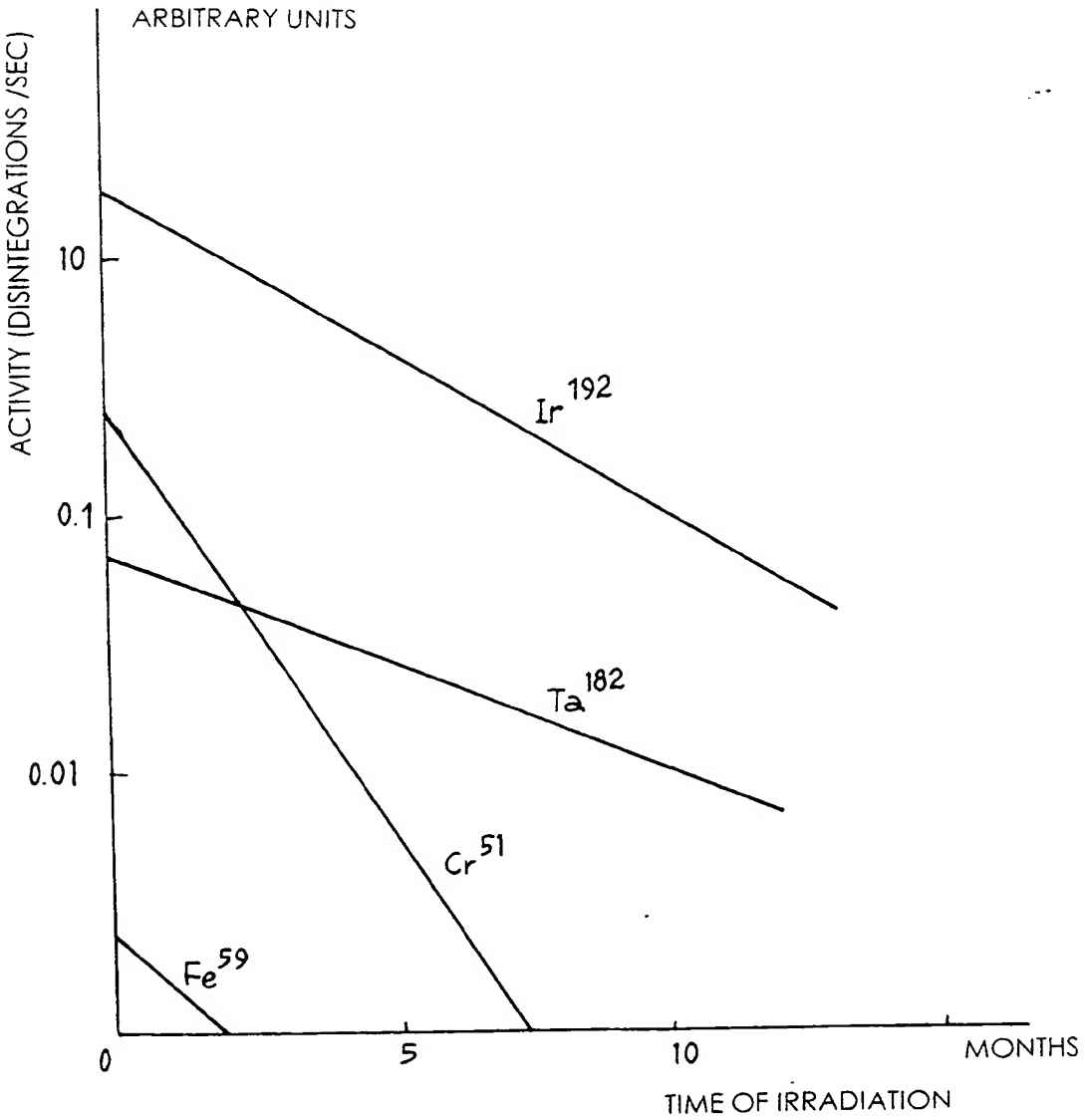

ARBITRARY UNITS
ACTIVITY (DISINTEGRATIONS /SEC)
10
0.1
0.01
Ir 192
Ta 182
Cr 51
Fe 59
0
5
10
MONTHS
TIME OF IRRADIATION

FIG. 4

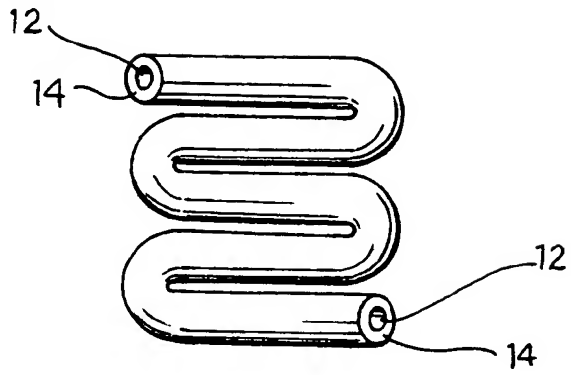
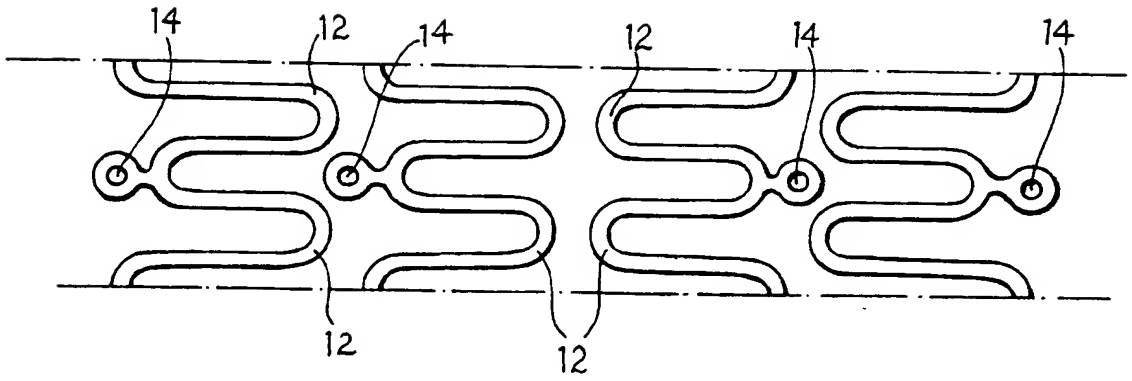


FIG. 5



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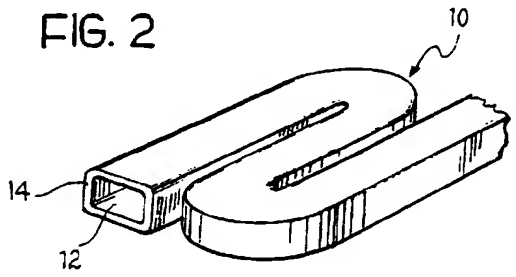

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EUROPEAN SEARCH REPORT

Application Number
EP 98 10 0010

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TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A61F
A61N

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	22 March 1999	Mary, C

CATEGORY OF CITED DOCUMENTS

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